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DEVELOPMENT OF NOVEL TOTAL INTRAVENOUS ANESTHESIA PROTOCOL USING CONSTANT RATE INFUSION IN GOATS DURING PAIN MANAGEMENT

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ABSTRACT

The study was aimed to develop a suitable total intravenous anesthesia protocol by comparative efficacy of three different combinations of detomidine, midazolam, propofol and ketamine in goats undergoing rumenotomy. In total, 18 female goats were divided into 3 treatment groups A, B and C comprising 6 animals each. In Group-A, after sedation with detomidine @ 2.5 µg/kg, induction was achieved with propofol @ 4 mg/kg and maintenance with constant rate infusion of (detomidine 2.5 µg/kg/hr + propofol 9.6 mg/kg/hr). Similarly, in Group-B, after sedation with midazolam @ 0.25 mg/kg, induction was done with ketamine @ 4 mg/kg and maintenance with infusion of (midazolam 0.25 mg/kg/hr + ketamine 2.4 mg/kg/hr). Whereas, in Group-C, after sedation with (detomidine1.25 µg/kg + midazolam 0.12 mg/kg), induction was done with (propofol 2 mg/kg + ketamine 2 mg/kg) and maintenance with combination of all drugs (detomidine 1.2 µg/kg/hr + midazolam 0.12 mg/kg/hr + propofol 4.5 mg/kg/hr + ketamine 1.2 mg/kg/hr) using a syringe-driving pump. Anesthetic, clinico-physiological and haematobiochemical parameters were evaluated. A better quality anesthesia with rapid and smooth induction, excellent muscle relaxation and rapid recovery was noticed in group C than group A and B. The statistical analysis indicated significant differences ($p<0.05$) for heart & respiratory rates, diastolic arterial pressure, partial pressure of oxygen and oxygen hemoglobin saturation among or within all groups except within group C. However, non-significant differences ($p>0.05$) were observed among or within all groups for packed cell volume, total erythrocyte count, total plasma protein and liver & renal function parameters. In conclusion, total intravenous anesthesia maintained with detomidine-midazolam-propofol-ketamine proved to be the best drug combinations taking into account the anesthetic, clinico-physiological and haematobiochemical parameters during pain management.

Keywords: Detomidine, midazolam, propofol, ketamine, constant rate infusion, goat.

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INTRODUCTION

Total intravenous anesthesia and inhalation anesthesia are two of the common types of general anesthesia. Total intravenous anesthesia provided better post-operative recovery with fewer post-operative side effects than inhalation anesthesia (Soliz *et al.,* 2017; Elbakry *et al.,* 2018; Iguchi *et al*., 2019). Total intravenous anesthesia referred to administration of solely an intravenous anesthetic agents via repeat bolus or constant rate infusion technique. The constant rate infusion technique was found better and safer than the repeat bolus infusion technique (Njoku, 2015). Ketamine, thiopental, propofol, α-2 agonists, opioids and lidocaine were reported as most commonly used intravenous anesthetic or sedative agents (Beths, 2017). Among α-2 agonist, detomidine as compared with xylazine, produced good quality sedation and better plane of surgical anesthesia in horses treated with midazolam-ketamine (Smith *et al.,* 2020a). The administration of detomidine provided sedation suitable for a short, minimally invasive procedure in dogs (Messenger *et al.,* 2016), cats (Smith *et al.,* 2020b), alpacas (Chow *et al.,* 2020), horse (Seddighi *et al.,* 2019), donkeys (Lizarraga *et al.,* 2016) and rabbits (Williams *et al.,* 2017). Midazolam is imidazobenzodiazepine derivative that had been reported as sedative, muscle relaxant, anticonvulsant (Dzikiti *et al.,* 2009; Shyken *et al.,* 2019) and anti-epileptic drug (Hamano *et al.,* 2019) with minimum cardiovascular effects (Dzikiti *et al.,* 2009; Kropf *et al.,* 2018). Premedication with midazolam compared to ketamine alone was found to be associated with smooth induction and excellent muscle relaxation in ponies (Allison *et al.,* 2017). Propofol has proven to be the most suitable agent for total intravenous anesthesia protocol due to its hypnotic (Chen *et al.,* 2020; Parks *et al.,* 2016), anti-inflammatory (Zheng *et al.,* 2018) and non-cumulative effects. Propofol-based anesthesia was associated with improved survival and lower post-operative complications than desflurane based-anesthesia (Lai *et al.,* 2019; Lai *et al.,* 2020; Wu *et al.,* 2018). The ketamine has recently gained an increasing interest due to its wide

margin of safety, role in pain management (Cohen *et al.,* 2018; Schwenk *et al.,* 2018; Orhurhu *et al.,* 2019) and antidepressant effects (Zanos and Gould, 2018; Fukumoto *et al.,* 2017).

A most suitable sedative and anesthetic combination is need of all time to conduct a successful surgery in any specie. To the knowledge of the author, there is a scarcity of published data regarding total intravenous anesthesia (TIVA) protocol and its delivery by constant rate infusion in the small ruminant. The present project, therefore, was designed to develop a suitable total intravenous anesthesia protocol by comparative efficacy of three different combinations of detomidine, midazolam, propofol and ketamine using constant rate infusion in goats undergoing rumenotomy.

MATERIALS AND METHODS

Ethical approval: The Ethical Review Committee of University of Veterinary & Animal Sciences approved this study (No. DR/551).

Experimental design: The study was carried out on 18 goats aged between 09-12 months with average body weight of 26-32 kg. The clinico-physiological parameters were monitored regularly throughout the observation period. The goats were assessed to be in good health based on physical and haematobiochemical values. Feeding was withheld at least 12 hours but had access to water for up to 2 hours before anesthesia. An electronic scale was used to weigh the animals 30 min before the experiment. In total, 18 female goats were randomly divided into 3 treatment groups A, B and C comprising 6 animals each. Anesthesia was maintained for 60 min and rumenotomy was performed in all groups. An overview of preanesthetic and anesthetic medication is given below.

Pre-anesthetic and anesthetic medication using constant rate infusion in goats.

Groups	Premedication(IM)	Induction (I/V)	Maintenance (I/V)
Group A	Detomidine @ 2.5 µg/kg	Propofol @ 4 mg/kg	Detomidine @ 2.5 µg/kg/hr + propofol @ 0.16 mg/kg/min
Group B	Midazolam @ 0.25 mg/kg	Ketamine @ 4 mg/kg	Midazolam @ 0.25 mg/kg/hr + ketamine Hcl @ 0.04 mg/kg/min
Group C	Detomidine @ 1.2 µg/kg + Midazolam @ 0.12 mg/kg	Propofol @ 2 mg/kg + ketamine @ 2 mg/kg	Detomidine @ 1.2 µg/kg/hr + midazolam @ 0.12 mg/kg/hr + propofol @ 0.075 mg/kg/min + ketamine @ 0.02 mg/kg/min

Detomidine; Domosedan injection, Orion Corporation, Finland
Midazolam; Dormicum injection, Fontenay-sous-Bois, France
Propofol ; Fresofol 1 % injection, Fresenius Kabi, Austria
Ketamine ; Ketalite injection, Elice Pharma, Pakistan

Surgical procedure: The animals were prepared aseptically for rumenotomy. After aseptic preparation of the operative site, rumenotomy was performed through a paramedian incision, using the technique described by Baird (2013). A vertical skin incision approximately 10 cm in length was given on left mid flank starting just ventral to lumber vertebrae. The subcutaneous tissue, external & internal abdominal oblique muscle, transverse abdominis muscle, deep iliac fascia and parietal layer of peritoneum were incised along the same line. The rumen was exteriorized and packed off with sterilized gauze. A vertical incision approximately 8 cm in length was given over the least vascular portion of greater curvature of rumen. After this, the rumen was explored to remove foreign materials like plastic bags. The rumenotomy incision was closed using vicryle # 2 with a double layer Cushing pattern. The laparotomy incision was sutured in three layers. The peritoneum along-with muscles were closed in first layer using vicryle # 2 in a simple continuous pattern. Similarly, the subcutaneous tissues were sutured in second layer using vicryle # 2 in simple continuous fashion. The skin was sutured using monofilament silk # 2 in a simple interrupted fashion. Anesthetic, clinico-physiological and haematobiochemical parameters were evaluated.

Parameters evaluated

Anesthesia parameters: The induction time, duration of anesthesia and total recovery time were recorded throughout the observation period. The qualities of induction, muscle relaxation and recovery were assessed following Ghurashi *et al.* (2016).

Clinico-physiological parameters: Heart & respiratory rates, rectal temperature, blood pressure (SAP, DAP, MAP), the partial pressure **(**PaO2, PaCO2) and haemoglobin saturation (SpO2) were monitored at 0 min

before treatment, 1 min after induction and thereafter, every 10-minute intervals during maintenance of anesthesia. Littman stethoscope (Littman Classic II, USA) was used to monitor the heart rate and Medicare digital thermometer (distributed by MANA & Co, Pakistan) was used to measure the rectal temperature. Systolic, diastolic and mean arterial pressure were measured by placing the non-invasive blood pressure monitor (Surgivet; Smith Medical PM, Inc., Waukesha, USA) around the antebrachium of left forelimb. Similarly, haemoglobin oxygen saturation was measured by placing the pulse oxymeter (Nonin Medical Inc., Minneapolis, USA) around the tongue. Arterial blood samples were collected anaerobically into 2 ml heparinized syringes by inserting 20-gauge catheter in the left auricular artery and the partial pressure of oxygen and carbon dioxide were measured by blood gas analyzer (i15 Vet Eden Shenzhen, China).

Haematobiochemical parameters: Blood samples (Approx. 5 ml) were collected in plain tubes via jugular vein puncturing with 23-G needle at 0, 15, 30 and 60 min during the observation period. After collection, the blood was centrifuged to harvest the serum and stored at -20 °C. Samples, thereafter, were delivered to quality operation laboratory (WTO, UVAS, Pakistan) for hematological and biochemical analysis. The PCV, TEC, TLC and hemoglobin concentration were measured using hematology analyzer (Beckman coulter, Fullerton, CA). Serum ALT, AST, ALP, BUN and creatinine were measured using autoanalyser (BT-3000, Biotecnica, Italy). The blood glucose concentration was measured using glucose meter (Accu- Chek, Roche Diagnostic Auckland, New Zealand). The cortisol level was measured using an enzyme-immunoassay technique with serial number EIA-1887 (DRG Diagnostic, DRG instrument GMBH, Murbarg, Germany).

Statistical Analysis: Statistical analysis was performed using the One-Way Analysis Of Variance in Statistical Analysis Software (SAS) 9.1 version at ($p<0.05$). Significant means at different time intervals were compared through Duncan's Multiple Range Test. Fisher's Least Significant Difference Test was used to compare significant means among the treatment groups at probability level of 0.05.

RESULTS

Evaluation of anesthetic parameters: The comparison among the treatment groups indicated significant differences ($p<0.05$) for sedation, analgesia, induction, muscle relaxation, recovery, induction time, duration of anesthesia and total recovery time (Table 1). The higher sedation scores were observed in group C and A compared to group B. Similarly, an excellent analgesia and muscle relaxation quality scores were noticed in the animals received the treatment C than those received the treatment A and B. Moreover, smooth induction and smooth recovery quality scores were also found in the animals received the treatment C compared to those received the treatment A and B. The animals receiving the treatment C resulted in minimum induction time, maximum duration of anesthesia and prolonged recovery time that showed significant ($p<0.05$) difference from those received the treatment A and B.

Evaluation of physiological parameters: The comparison among the treatment groups indicated significant differences ($p<0.05$) for heart & respiratory rates and non-significant differences ($p>0.05$) were observed for rectal temperature after treatment (Table 2). The highest heart and respiratory rates were found in the animals receiving the treatment B than those received the treatments C and A at different time intervals after treatment. The highest rectal temperature, in contrast, was found in group C than group A and B. The statistical analysis indicated a non-significant ($p>0.05$) decreasing trend of heart & respiratory rates within group C and a significant ($p<0.05$) decreasing trend within group A. A significant ($p<0.05$) increasing trend, in contrast, was noticed within group B. The rectal temperature also showed a non-significant ($p>0.05$) decreasing trend within all groups (Table 2).

Evaluation of blood pressure: Effects of various treatments on blood pressure are presented in Table 3. The comparison among the treatment groups indicated significant differences ($p<0.05$) for arterial blood pressure. The minimum deviation from baseline values were found in group C than group A and B. The goats receiving the treatment C showed higher values of systolic, diastolic and mean arterial pressure that are close to normal physiological values compared with those received the treatments A and B. Statistically, a significant ($p<0.05$) decreasing trends of systolic, diastolic and mean arterial pressure were observed within all groups except the diastolic arterial pressure within group C (Table 3).

Evaluation of oxygen haemoglobin saturation, the partial pressure of oxygen and carbon dioxide: The comparison among the treatment groups indicated significant differences ($p<0.05$) for the partial pressure of oxygen, carbon dioxide and oxygen haemoglobin saturation at different time intervals except the partial pressure of oxygen at 1 and 10 min after treatment (Table 4). The animals received the treatment C showed a minimum deviation from normal physiological values compared to those received the treatments A and B. The highest values of the partial pressure of oxygen and oxygen haemoglobin saturation were found in group C compared to group A and B. Whereas, the highest values of the partial pressure of carbon dioxide were noticed in

group A than group B and C. The statistical analysis revealed a non-significant ($p>0.05$) decreasing trend of partial pressure of oxygen and oxygen haemoglobin saturation within group C and a significant ($p<0.05$) decreasing trend within groups A and B with a peak decrease at 60 min. A significant ($p<0.05$) increasing trend of the partial pressure of carbon dioxide, however, was observed within all groups with peak increase at 60 min (Table 4).

Evaluation of haematological parameters: Effects of various anesthetic protocols on haematological parameters are presented in Table 5. The results indicated non-significant ($p>0.05$) effects of all treatment protocols on total erythrocyte count and packed cell volume among or within groups during the observation period. Moreover, non-significant ($p>0.05$) effects among the groups and significant ($p<0.05$) effects within groups were noticed for total leukocyte count. The goats receiving the treatment C showed a minimum deviation from normal baseline values compared to those received the treatment A and B for all haematological parameters. The highest values of packed cell volume were noticed in group C than groups A and B. The highest values of total erythrocyte and leukocyte count, in contrast, were found in group B than groups A and C (Table 5).

Evaluation of biochemical parameters: The results indicated significant ($p<0.05$) impacts of all treatment protocols on serum glucose and cortisol level and non-significant ($p>0.05$) impacts on total plasma protein among or within groups during the observation period (Table 6). The minimum deviation from baseline values, however, were observed in the animals receiving the treatment C than those received the treatments A and B for all biochemical parameters. The highest values of serum glucose were found in group A than group B and C at 15, 30 and 60 min following the treatment. The highest values of total plasma protein, in contrast, were observed in group C compared to group A and B. The highest cortisol level was observed in group B than group A and C.

Table 3. Effects of various anesthetic protocols on arterial blood pressure using constant rate infusion in goats undergoing rumenotomy.

Parameters	Time	Treatment groups			p-value
		A	B	C	
SAP (mm Hg)	0 min	120.00 ± 1.15^{aA}	118.00 ± 1.65^{aA}	121.00 ± 1.15^{aA}	0.3025
	1 min	113.00 ± 1.15^{bB}	112.00 ± 1.65^{bB}	118.00 ± 1.15^{abA}	0.0141
	10 min	111.00 ± 1.15^{bcB}	110.00 ± 1.65^{bcB}	117.00 ± 1.15^{bA}	0.0044
	20 min	110.00 ± 1.15^{bcdB}	109.00 ± 1.65^{bcB}	117.00 ± 1.15^{bA}	0.0014
	30 min	108.00 ± 1.15^{cdeB}	107.00 ± 1.65^{bcB}	116.00 ± 1.15^{bA}	0.0004
	40 min	107.00 ± 1.15^{deB}	106.00 ± 1.65^{cB}	116.00 ± 1.15^{bA}	0.0001
	50 min	106.00 ± 1.15^{eB}	105.00 ± 1.65^{cB}	115.00 ± 1.15^{bA}	0.0001
	60 min	106.00 ± 1.15^{eB}	105.00 ± 1.65^{cB}	115.00 ± 1.15^{bA}	0.0001
	p-value	<.0001	<.0001	0.0156	
DAP (mm Hg)	0 min	80.00 ± 1.71^{aA}	78.00 ± 1.39^{aA}	81.00 ± 1.65^{aA}	0.4195
	1 min	73.00 ± 1.71^{bB}	72.00 ± 1.39^{bB}	78.00 ± 1.65^{abA}	0.0385
	10 min	71.00 ± 1.71^{bcB}	70.00 ± 1.39^{bcB}	77.00 ± 1.65^{abA}	0.0148
	20 min	70.00 ± 1.71^{bcB}	69.00 ± 1.39^{bcdB}	77.00 ± 1.65^{abA}	0.0055
	30 min	68.00 ± 1.71^{bcB}	67.00 ± 1.39^{cdB}	76.00 ± 1.65^{abA}	0.0021
	40 min	67.00 ± 1.71^{cB}	66.00 ± 1.39^{cdB}	76.00 ± 1.65^{abA}	0.0008
	50 min	66.00 ± 1.71^{cB}	65.00 ± 1.39^{dB}	75.00 ± 1.65^{bA}	0.0008
	60 min	66.00 ± 1.71^{cB}	65.00 ± 1.39^{dB}	75.00 ± 1.65^{bA}	0.0008
	p-value	<.0001	<.0001	0.2304	
MAP (mm Hg)	0 min	93.33 ± 0.93^{aA}	91.33 ± 1.01^{aA}	94.33 ± 1.18^{aA}	0.1520
	1 min	86.33 ± 0.93^{bB}	85.33 ± 1.01^{bB}	91.33 ± 1.18^{abA}	0.0022
	10 min	84.33 ± 0.93^{bcB}	83.33 ± 1.01^{bcB}	90.33 ± 1.18^{bA}	0.0005
	20 min	83.33 ± 0.93^{cdB}	82.33 ± 1.01^{bcdB}	90.33 ± 1.18^{bA}	0.0001
	30 min	81.33 ± 0.93^{deB}	80.33 ± 1.01^{cdeB}	89.33 ± 1.18^{bA}	<.0001
	40 min	80.33 ± 0.93^{eB}	79.33 ± 1.01^{deB}	89.33 ± 1.18^{bA}	<.0001
	50 min	79.33 ± 0.93^{eB}	78.33 ± 1.01^{eB}	88.33 ± 1.18^{bA}	<.0001
	60 min	79.33 ± 0.93^{eB}	78.33 ± 1.01^{eB}	88.33 ± 1.18^{bA}	<.0001
	p-value	<.0001	<.0001	0.0196	

Different superscripts (A-B) in column indicate significant differences ($p<0.05$) among the groups
Different superscripts (a-e) in row indicate significant differences ($p<0.05$) within groups

Table 1. Mean (±S.E.) values of various anesthetic parameters after administration of detomidine, midazolam, propofol and ketamine using constant rate infusion in goats undergoing rumenotomy.

Treatment groups	Sed. Score	Anal. Score	Ind. Score	M. Relax Score	Recov. Score	I.T (Sec)	D.o.A (min)	T.R.T (min)
A **Deto + Prop**	4.00±0.00^{a}	2.00±0.00^{a}	1.00±0.00^{b}	2.00±0.00^{b}	1.00±0.00^{b}	25.33±1.20^{b}	66.33±0.42^{b}	83.12± 0.51^{b}
B **Mid + Ket**	3.00±0.00^{b}	2.00±0.00^{a}	2.00±0.00^{a}	3.00±0.00^{a}	2.00±0.00^{a}	35.00±1.15^{a}	63.50±0.43^{c}	78.08± 0.87^{c}
C **Det+Mid + Prop+ Ket**	4.00±0.00^{a}	1.00±0.00^{b}	1.00±0.00^{b}	1.00±0.00^{c}	1.00±0.00^{b}	16.33±1.12^{c}	70.50±0.62^{a}	98.49± 1.38^{a}
p-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

Deto is detomidine; mid is midazolam; Prop is propofol; Ket is ketamine; Sed. is sedation; Anal is analgesia; Ind. is induction; M. Relax is muscle relaxation; I.T is induction time; Recov. is recovery; D.o.A is duration of anesthesia; T.R.T is total recovery time; Sec is second and min is minute.

Table 2. Effects of various anesthetic protocols on clinico-physiological parameters using constant rate infusion in goats undergoing rumenotomy.

Parameters	Time	Treatment groups			p-value
		A	B	C	
Heart Rate (beats/min)	0 min	61.00±0.37^{Aa}	62.00±0.37^{eA}	62.00±0.73^{aA}	0.3147
	1 min	57.00±0.37^{Bc}	67.00±0.37^{dA}	61.33±0.56^{abB}	<.0001
	10 min	56.00±0.37^{bcC}	69.00±0.37^{cA}	61.00±0.37^{abB}	<.0001
	20 min	55.00±0.37^{cdC}	70.00±0.37^{cA}	61.00±0.37^{abB}	<.0001
	30 min	54.00±0.37^{deC}	72.00±0.37^{bA}	61.00±0.37^{abB}	<.0001
	40 min	53.00±0.37^{efC}	73.00±0.37^{abA}	60.50±0.43^{bB}	<.0001
	50 min	52.00±0.37^{fgC}	73.00±0.37^{abA}	60.17±0.31^{bB}	<.0001
	60 min	51.00±0.37^{Gc}	74.00±0.37^{aA}	60.00±0.26^{bB}	<.0001
	p-value	<.0001	<.0001	0.0649	
Respiratory Rate (breaths/min)	0 min	15.00±0.37^{aA}	15.00±0.37^{fA}	15.00±0.37^{aA}	1.0000
	1 min	13.00±0.37^{bB}	17.00±0.37^{eA}	14.00±0.37^{bB}	<.0001
	10 min	12.00±0.37^{bcC}	18.00±0.37^{deA}	14.33±0.33^{abB}	<.0001
	20 min	12.00±0.37^{bcC}	18.00±0.37^{deA}	14.17±0.31^{abB}	<.0001
	30 min	11.00±0.37^{cdC}	19.00±0.37^{cdA}	14.00±0.26^{bB}	<.0001
	40 min	11.00±0.37^{cdC}	20.00±0.37^{bcA}	13.83±0.31^{bB}	<.0001
	50 min	10.00±0.37^{dC}	21.00±0.37^{abA}	13.67±0.33^{bB}	<.0001
	60 min	10.00±0.37^{dC}	22.00±0.37^{aA}	13.50±0.22^{bB}	<.0001
	p-value	<.0001	<.0001	0.0597	
Rectal Temp. (°F)	0 min	102.05±0.02	102.05±0.02	102.05±0.02	1.0000
	1 min	101.95±0.02	102.00±0.04	102.00±0.00	0.3911
	10 min	101.95±0.02	101.98±0.02	102.00±0.04	0.5121
	20 min	101.93±0.06	101.95±0.02	101.98±0.02	0.6603
	30 min	101.93±0.06	101.95±0.02	101.97±0.02	0.8399
	40 min	101.90±0.04	101.93±0.03	101.97±0.02	0.4134
	50 min	101.90±0.09	101.93±0.03	101.95±0.02	0.8190
	60 min	101.90±0.04	101.93±0.02	101.95±0.02	0.5310
	p-value	0.4921	0.0581	0.0943	

Different superscripts (A-C) in column reveal significant differences ($p<0.05$) among the groups
Different superscripts (a-g) in row reveal significant differences ($p<0.05$) within groups

Table 4. Effects of various anesthetic protocols on the partial pressure of oxygen, carbon dioxide and oxygen hemoglobin saturation using constant rate infusion in goats undergoing rumenotomy.

Parameters	Time	Treatment groups			p-value
		A	B	C	
PaO2 (mm Hg)	0 min	82.00±0.73^{aA}	81.00±0.93^{aA}	80.00±1.10^{aA}	0.3419
	1 min	77.17±0.60^{bA}	77.00±1.10^{bA}	78.83±1.05^{aA}	0.3398
	10 min	74.50±0.76^{cB}	76.00±1.10b^{AB}	78.17±1.01^{aA}	0.0519
	20 min	73.50±0.76^{cdB}	76.00±1.10^{bAB}	78.17±1.01^{aA}	0.0135
	30 min	73.67±0.67^{cdB}	75.00±1.10^{bB}	78.00±0.93^{aA}	0.0130
	40 min	72.83±0.65^{cdB}	75.00±1.10^{bB}	77.83±0.83^{aA}	0.0041
	50 min	72.00±0.73^{dB}	74.00±1.10^{bB}	77.67±0.76^{aA}	0.0013
	60 min	72.00±0.73^{dB}	74.00±1.10^{bB}	77.33±0.61^{aA}	0.0015
	p-value	<.0001	0.0010	0.5886	
PaCO2 (mm Hg)	0 min	34.00±0.73^{fA}	33.00±0.73^{eA}	32.00±0.63^{eA}	0.1639
	1 min	43.67±0.84^{eA}	41.50±0.76^{dA}	35.67±0.67^{bC}	<.0001
	10 min	49.33±0.67^{dA}	45.67±0.88^{cB}	35.83±0.70^{bC}	<.0001
	20 min	53.67±0.67^{cA}	50.50±0.76^{bB}	36.50±0.76^{bC}	<.0001
	30 min	54.00±0.86^{cA}	51.00±0.58^{bB}	37.17±0.87^{abC}	<.0001
	40 min	56.00±0.86^{bcA}	53.67±0.71^{aA}	37.83±0.95^{abB}	<.0001
	50 min	57.33±0.84^{abA}	54.50±0.76^{aB}	38.17±0.79^{abC}	<.0001
	60 min	58.50±0.76^{aA}	55.83±0.95^{aB}	39.17±0.79^{aC}	<.0001
	p-value	<.0001	<.0001	<.0001	
SpO2 (%)	0 min	91.00±0.86^{aA}	90.00±0.73^{aA}	92.00±0.52^{aA}	0.1758
	1 min	86.67±0.99^{bB}	87.33±0.84^{bB}	90.83±0.48^{abA}	0.0047
	10 min	86.00±0.73^{bB}	86.50±0.67^{bcB}	90.50±0.62^{abA}	0.0005
	20 min	85.67±0.71^{bB}	86.33±0.99^{bcdB}	90.50±0.62^{abA}	0.0011
	30 min	85.17±1.08^{bcB}	85.17±0.83^{bcdB}	90.00±0.63^{bA}	0.0015
	40 min	84.67±0.92^{bcB}	84.67±0.67^{cdB}	89.83±0.60^{bA}	0.0002
	50 min	84.17±0.70^{bcB}	84.17±0.83^{cdB}	89.67±0.49^{bA}	<.0001
	60 min	83.00±0.52^{cB}	83.83±0.87^{dB}	89.50±0.62^{bA}	<.0001
	p-value	<.0001	<.0001	0.0829	

Different superscripts (A-C) in column show significant differences ($p<0.05$) among the groups
Different superscripts (a-f) in row show significant differences ($p<0.05$) within groups

Evaluation of liver function parameters: The results indicated non-significant ($p>0.05$) effects of all treatment protocols on ALT, AST and ALP at different time intervals following treatments (Table 6). The minimum deviation from baseline values, however, were observed in group C than group A and B. The highest values of ALT, AST and ALP were found in group B compared to group C and A at 15 and 30 min during the observation period.

Evaluation of renal function parameters: Of the renal function parameters assessed, the statistical analysis also indicated non-significant ($p>0.05$) effects of all treatment protocols on creatinine and blood urea nitrogen during the observation period (Table 6). The animals received the treatment C showed a minimum deviation from normal baseline values compared to those received the treatments A and B. The highest values of creatinine were found in group B than group A and C at 15, 30 and 60 min after treatment.

Table 5. Effects of various anesthetic protocols on haematological parameters using constant rate infusion in goats undergoing rumenotomy.

Parameters	Time	Treatment groups			p-value
		A	B	C	
Packed cell volume (%)	0 min	28.15±0.33^{aA}	28.68±0.36^{aA}	28.45±0.31^{aA}	0.5349
	15 min	27.62±0.30^{abA}	28.13±0.28^{abA}	28.16±0.24^{aA}	0.3263
	30 min	27.34±0.15^{bB}	27.89±0.22^{bAB}	27.99±0.25^{aA}	0.0912
	60 min	27.38±0.15^{bA}	27.69±0.09^{bA}	27.78±0.25^{aA}	0.2649

	p-value	0.1116	0.0637	0.3462	
Haemoglobin concentration (g/dl)	0 min	8.24±0.08^{aA}	8.20±0.06^{bA}	8.17±0.06^{aA}	0.7550
	15 min	8.15±0.04^{abA}	8.27±0.06^{abA}	8.11±0.05^{aA}	0.1501
	30 min	8.06±0.03^{bB}	8.39±0.06^{aA}	8.07±0.05^{aB}	0.0003
	60 min	8.03±0.02^{bB}	8.42±0.06^{aA}	8.04±0.05^{aB}	<.0001
	p-value	0.0246	0.0590	0.4068	
Total erythrocyte count (10^{12}/l)	0 min	13.25±0.05^{aB}	13.78±0.20^{aA}	13.55±0.17^{aAB}	0.0833
	15 min	12.91±0.17^{aA}	13.46±0.25^{aA}	13.29±0.17^{aA}	0.1764
	30 min	12.84±0.17^{aA}	13.25±0.31^{aA}	13.21±0.17^{aA}	0.3824
	60 min	12.77±0.17^{aA}	13.19±0.28^{aA}	13.19±0.17^{aA}	0.3085
	p-value	0.1477	0.3973	0.4403	
Total leukocyte count (10^{9}/l)	0 min	10.73±0.07^{dA}	10.76±0.07^{cA}	10.74±0.09^{bA}	0.9432
	15 min	11.16±0.12^{cA}	11.19±0.16^{bcA}	11.02±0.18^{bA}	0.7072
	30 min	11.56±0.13^{bAB}	11.59±0.18^{bA}	11.10±0.17^{bB}	0.0800
	60 min	12.12±0.09^{aA}	12.33±0.18^{aA}	12.04±0.16^{aA}	0.3962
	p-value	<.0001	<.0001	<.0001	

Different superscripts (A-B) in column indicate significant differences ($p<0.05$) among the groups
Different superscripts (a-d) in row indicate significant differences ($p<0.05$) within groups

Table 6. Effects of various anesthetic protocols on biochemical parameters using constant rate infusion in goats undergoing rumenotomy.

Parameters	**Time**	**Treatment groups**			**p-value**
		A	**B**	**C**	
Serum glucose (mg/dl)	0 min	49.33±1.28^{bAB}	50.83±1.17^{cA}	47.17±1.08^{cB}	0.1203
	15 min	73.33±1.82^{aA}	65.67±1.71^{bB}	64.67±0.67^{bB}	0.0017
	30 min	74.67±1.38^{aA}	70.83±1.87^{aAB}	68.67±0.67^{aB}	0.0255
	60 min	75.83±0.91^{aA}	72.50±1.48^{aB}	70.33±0.80^{aB}	0.0103
	p-value	<.0001	<.0001	<.0001	
Total plasma protein (g/dl)	0 min	6.27±0.01^{aA}	6.29±0.01^{aA}	6.28±0.01^{aA}	0.2956
	15 min	6.26±0.00^{aA}	6.27±0.00^{abA}	6.27±0.01^{aA}	0.1657
	30 min	6.26±0.00^{aB}	6.26±0.00^{bAB}	6.27±0.00^{aA}	0.0698
	60 min	6.26±0.00^{aB}	6.26±0.00^{bAB}	6.27±0.00^{aA}	0.0814
	p-value	0.1144	0.0653	0.4026	
Cortisol level (ng/ml)	0 min	15.01±0.16^{dA}	15.32±0.10^{dA}	15.19±0.06^{dA}	0.1947
	15 min	28.22±0.57^{cA}	29.68±0.52^{cA}	19.74±0.40^{cB}	<.0001
	30 min	34.47±0.62^{bA}	35.96±0.57^{bA}	21.75±0.57^{bB}	<.0001
	60 min	37.47±0.60^{aB}	39.46±0.69^{aA}	22.62±0.63^{aC}	<.0001
	p-value	<.0001	<.0001	<.0001	
ALT (U/L)	0 min	11.33±0.42^{bA}	11.67±0.42^{bA}	12.00±0.37^{bA}	0.5207
	15 min	11.83±0.31^{abA}	12.50±0.43^{abA}	12.50±0.22^{abA}	0.2875
	30 min	12.33±0.42^{abA}	13.17±0.48^{aA}	12.83±0.31^{abA}	0.3187
	60 min	12.83±0.40^{aA}	13.50±0.56^{aA}	13.00±0.26^{aA}	0.5296
	p-value	0.0712	0.0607	0.1129	
AST (U/L)	0 min	20.67±0.33^{bA}	21.00±0.26^{bA}	21.33±0.21^{aA}	0.2548
	15 min	21.17±0.31^{abA}	21.33±0.33^{abA}	21.67±0.21^{aA}	0.4771
	30 min	21.50±0.22^{abA}	21.83±0.31^{abA}	21.67±0.21^{aA}	0.6514
	60 min	21.83±0.31^{aA}	22.00±0.26^{aA}	21.83±0.31^{aA}	0.8977
	p-value	0.0645	0.0900	0.5230	
ALP (U/L)	0 min	298.17±0.79^{bA}	299.83±0.79^{bA}	300.33±0.67^{aA}	0.1375
	15 min	299.50±0.67^{abA}	300.50±0.34^{abA}	300.83±0.40^{aA}	0.1719
	30 min	300.00±0.58^{abB}	301.33±0.33^{abA}	301.00±0.37^{aAB}	0.1156
	60 min	300.67±0.56^{aA}	301.67±0.42^{aA}	301.17±0.31^{aA}	0.3052
	p-value	0.0804	0.0766	0.6089	
BUN (mg/dl)	0 min	15.00±0.37^{bA}	14.50±0.43^{bA}	15.50±0.22^{aA}	0.1639
	15 min	15.33±0.21^{abA}	15.00±0.37^{abA}	15.83±0.31^{aA}	0.1783

	30 min	15.83±0.31^{abA}	15.33±0.21^{abA}	16.00±0.26^{aA}	0.2063
	60 min	16.17±0.31^{aA}	15.83±0.31^{aA}	16.17±0.17^{aA}	0.6089
	p-value	0.0587	0.0687	0.2846	
	0 min	1.54±0.01^{bA}	1.55±0.01^{aA}	1.55±0.00^{aA}	0.1495
Creatinine	15 min	1.55±0.00^{abB}	1.56±0.00^{aA}	1.55±0.00^{aAB}	0.1244
(mg/dl)	30 min	1.55±0.00^{abA}	1.56±0.00^{aA}	1.55±0.00^{aA}	0.5546
	60 min	1.56±0.00^{aA}	1.57±0.01^{aA}	1.56±0.00^{aA}	0.1232
	p-value	0.0782	0.1596	0.4575	

Different superscripts (A-C) in column reveal significant differences ($p<0.05$) among the groups
Different superscripts (a-d) in row reveal significant differences ($p<0.05$) within groups

DISCUSSION

The present study was planned to develop a suitable total intravenous anesthesia protocol by comparative efficacy of three different combinations of detomidine, midazolam, propofol and ketamine using constant rate infusion in goats undergoing rumenotomy.

In the present study, total intravenous anesthesia maintained with detomidine-midazolam-propofol-ketamine produced comparatively deep sedation and excellent analgesia than detomidine-propofol and midazolam-ketamine. The deep sedation and excellent analgesia remained consistent throughout the 60-minute maintenance period. It may be attributed to the fact that, different drugs when injected in combination, strengthened the sedative and analgesic effects of the single drug. These findings are similar to that recorded by de Carvalho *et al.* (2016) who reported that xylazine in combination with methadone, morphine and tramadol provided better sedation and analgesia than xylazine alone in sheep. These results were also supported by findings of Sabertanha *et al.* (2019) who demonstrated that infusion of mixture of ketamine-propofol provided better analgesia compared to propofol alone.

The combination of detomidine-midazolam-propofol-ketamine also resulted in satisfactory anesthesia with comparatively rapid & smooth induction, excellent muscle relaxation and smooth recovery along with minimal effects on cardiopulmonary function than detomidine-propofol and midazolam-ketamine. It may be attributed to the fact that, detomidine and ketamine present in the mixture produced strong analgesic effects, whereas, propofol in the mixture resulted in smooth induction and rapid recovery that ultimately led to satisfactory anesthesia. These findings were similar to those recorded by Wamaitha *et al.* (2019) who demonstrated that propofol in ketofol resulted in smooth induction & rapid recovery, whereas, ketamine in mixture provided the analgesic effects. These results were also supported by the findings of Kalaiselvan *et al.* (2020) who reported that anesthesia maintained with constant rate infusion of dexmedetomidine-butorphenol-ketamine-propofol provided satisfactory anesthesia with minimal cardiorespiratory effects in canine orthopaedic patients. Similar findings were also reported in goats (Sengar *et al.,* 2020), impala (Buck *et al.,* 2017), dogs (Thejasree *et al.,* 2018) and horses (Umar *et al.,* 2014).

In the present study, the combined administration of detomidine-midazolam-propofol-ketamine resulted in comparatively more stable cardiopulmonary function than detomidine-propofol and midazolam-ketamine. It may be attributed to the fact that combination of various drugs resulted in fewer adverse effects compared with either drug alone. Saikia *et al*. (2016) also reported that ketamine in combination with propofol, α-2 agonists and benzodiazepines produced minimum adverse effects compared with ketamine alone. The reduction in heart rate observed in the present study may be due to depressive cardiovascular effects of detomidine compared to propofol and ketamine. The fact is, cardiovascular stimulatory effects of propofol and ketamine were mainly antagonized with depressive effect of detomidine resulting in net bradycardia as that of reported by Hopster *et al.* (2014). The reduction in heart rate was reported as a common side effect of xylazine and detomidine in sheep (de Carvalho *et al.,* 2016; de Moura *et al.,* 2018). The reduction in rectal temperature could have resulted due to depressive effects of drugs on thermoregulatory set point or might be due to decreased muscular activity during anesthesia as that of reported by EL-Kammar *et al.* (2014). Similar findings were also recorded by Sengar *et al.* (2020) who reported non-significant reduction in rectal temperature after administration of midazolam-propofol-ketamine in atropinized goats. Maravi *et al.* (2018) also reported non-significant decrease in rectal temperature after administration of detomidine-propofol in atropinized goats. These results were also supported by the findings of Yohannes (2018) who demonstrated non-significant reduction in rectal temperature after administration of ketamine-xylazine in dogs. Hypothermia was reported as a common complication of detomidine in goats (Tunio *et al.,* 2016) and cattle (Gnanasekar *et al.,* 2019).

The combined administration of detomidine-midazolam-propofol-ketamine also resulted in minimal changes in systolic, diastolic and mean arterial pressure than detomidine-propofol and midazolam-ketamine. It may be due to the fact that, the combined administration of propofol and ketamine showed antagonistic effects on arterial blood pressure resulting in improved

cardiovascular stability. Similar findings were also recorded by Uludağ *et al.* (2020) who reported that midazolam-ketamine provided better haemodynamic stability than midazolam-propofol with minimal changes in systolic and diastolic arterial pressure. These results were also similar to those recorded by Kumar *et al.* (2014) who reported that goats treated with dexmedetomidine-propofol and dexmedetomidine-ketamine produced excellent sedation and muscle relaxation along-with significant reduction in mean arterial pressure.

The combined administration of detomidine-midazolam-propofol-ketamine likewise, blood pressure, also resulted in better oxygen saturation with no respiratory cessation than detomidine-propofol and midazolam-ketamine, hence, it may be preferred in cases with compromised cardiovascular and respiratory function. The changes in arterial blood-gas observed in the present study were in agreement with changes previously reported in dogs (Seo *et al.,* 2015; Lee *et al.,* 2015). These results were also supported by the findings of Velázquez-Delgado *et al.* (2021) who demonstrated that administration of propofol-fentanyl-lidocaine-ketamine showed no respiratory cessation but better oxygen saturation in goats undergoing abomasotomy.

In the present study, total intravenous anesthesia maintained with combination of detomidine-midazolam-propofol-ketamine resulted in a better haematobiochemical stability than detomidine-propofol and midazolam-ketamine. It could be obtained probably due to opposing hemodynamic effects of propofol and ketamine that ultimately lead to minimal adverse effects. The reduction in hemoglobin concentration, total erythrocyte count and packed cell volume observed in the present study may be attributed to the sequestration of red blood cells in the spleen as that of reported in some earlier studies (Singh *et al.,* 2013; Kumar *et al.,* 2014). These results are also similar to those recorded by Yohannes (2018) who reported non-significant reduction in hemoglobin concentration, total erythrocyte count and packed cell volume in dogs treated with ketamine-xylazine. These results were also supported by the findings of Sengar *et al.* (2020) who observed non-significant reduction in hemoglobin concentration, total erythrocyte count and packed cell volume in goats treated with midazolam-propofol-ketamine.

The increased blood glucose level observed in the present study may be due to hyperglycemic effects of ketamine, detomidine and propofol during rumenotomy. Hyperglycemia had been reported as common classical complication of detomidine (Kritchevsky *et al*., 2020; Box *et al.,* 2021), ketamine (Sahoo *et al.,* 2018), propofol (Maeda *et al.,* 2018) and daizepam (Mohammed *et al.,* 2018). The increased level of glucose could have resulted due to surgical stress during rumenotomy as that of reported by Njoku *et al.* (2015) and Kisani *et al.* (2018). These findings are also in line with those recorded by Sengar *et al.* (2020) who observed significant increase in blood glucose level after administering midazolam-propofol-ketamine in atropinized goats.

The increased cortisol level observed in the present study might be due to surgical stress during rumenotomy as that of reported by Kisani *et al.* (2018) and Khoo *et al.* (2017). Moreover, the cortisol responses also indicated that stress response to surgical stimulation were more effectively suppressed after administering combination of detomidine-midazolam-propofol-ketamine than detomidine-propofol and midazolam-ketamine, hence, a preferred anesthesia. It could have resulted due to combined analgesic effects of detomidine, ketamine and midazolam, which in turn, decreased the cortisol secretion during rumenotomy. The stress response induced during superficial soft-tissue surgery was also attenuated by use of propofol-fentanyl anesthesia in piglets (Schöffmann *et al.,* 2009). Similar findings were also reported in goats after administration of different combinations of propofol, xylazine and ketamine (Okwudili *et al.,* 2014).

The increased ALT, AST and ALP level observed in the present study could have resulted due to the depressant effects of drugs on hepatic blood flow that may cause mild depression of liver resulting in increased liver enzymes. These findings are also in line with those recorded by Sengar *et al.* (2020) who observed non-significant increase in alanine aminotransferase and aspartate aminotransferase after administration of midazolam-propofol-ketamine in atropinized goats. Similar findings were also reported in dogs (Thejasree *et al.,* 2018). The increase in blood urea nitrogen and creatinine level may be due to cessation of renal blood flow that may cause mild depression of kidney, resulting in accumulation of nitrogenous substances in the blood. These results are also similar to those recorded by Sengar *et al.* (2020) who observed non-significant increase in blood urea nitrogen and creatinine level after administration of midazolam-propofol-ketamine in atropinized goats.

Conclusion: In conclusion, the total intravenous anesthesia maintained with detomidine-midazolam-propofol-ketamine produced a satisfactory anaesthesia with mild, transient changes in clinico-physiological and haematobiochemical parameters that remained within physiological limits.

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